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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,710	CHIU ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 13-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/3/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-6 and 13-16 are considered. Claims 1-6 and 14-16 are currently pending.

Although the amendment of 1 April 2002 states that Claim 13 is cancelled, it also asks for the consideration and allowance of that claim, and Claims 14-16, which were not cancelled and are dependent on Claim 13. Hence, the Examiner considered Claim 13 as if it were not cancelled. Applicant's are required to amend their Claims accordingly in response to this action.

Drawings

The drawings are objected to because the specification describes colors within the photographs, and such colors are not given in the drawings; hence, the Examiner cannot see what is described in the text of the specification. Moreover, the brief description of the drawings in the specification does not indicate Figure 1A and 1B, but Figure 1, top and bottom panel, and no Figure 2A or 2B is described in the brief description of the drawings. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 2 is objected to because of the following informalities: Claim 2 recites "the step of using cell labeling technique". The examiner suggests the use of an article. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 13-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention, and that, therefore, Applicant's claims are not enabled.

The Breadth of the Claims

Claims 1-6 and 13-16 are broad in scope. The following paragraphs will outline the full breadth of these claims.

Claims 1-6 encompass methods of improving any cardiac function in a patient with heart failure by the transplanting of any autologous bone marrow stromal cells (MSC) into any of the patient's myocardium to grow new muscle fibers, without eliciting any immune response or sacrificing any of the patient's skeletal muscle. Claim 2 adds any step of labeling the MSC to confirm survival and differentiation of such cells, and to identify the phenotype of such MSC by both morphology and any molecular markers. Claim 3 adds any step of examining the effects of the implanted MSC's microenvironment on their differentiation and any phenotype expression. Claim 4 adds the step of examining the functional contribution of any MSC implanted into any ischemic segment of the myocardium. Claim 5 limits the step of transplanting of any of Claims 1-4 to being effected in the myocardium, *in situ*, in the myocardium artery, or via catheter into the myocardium.

Claims 13-16 encompass methods of treating cardiac failure, comprising the steps of (i) retrieving any bone marrow from any patient, (ii) isolating MSC from the bone marrow, (iii) expanding MSC from the marrow, and (iv) transplanting the expanded MSC into any myocardium of the patient. Claim 14 limits the step of retrieving to including bone marrow

puncture. Claim 15 limits the step of transplanting to including infusion of the cells into any coronary circulation. Claim 16 limits the step of transplanting to transvenous catheter injection.

Because these claims are broad, encompassing the use of marrow stromal cells, which may be expanded in culture, and their administration to the coronary circulation, direct myocardial injection, and transvenous catheter injection to improve any cardiac function in patients with heart failure, and to treat cardiac failure itself, the disclosure provided by Applicants, in view of the prior art, must encompass a wide area of knowledge. In other words, those areas considered broad must be fleshed out to a reasonable extent so that one of skill in the art at the time of invention by Applicant (hereinafter the "Artisan"), would be able to practice the invention without an undue burden being imposed on such Artisan (undue burden). Such undue is generally found after an analysis of the of above-listed factors and a finding that the Artisan would have had to do a non-routine amount of experimentation because the invention claimed cannot be reasonably predicted to work, and the Artisan would have had to go about experimentation to find an embodiment of the invention that would work, effectively reducing Applicant's claimed invention to practice himself.

The Nature of the Invention

The invention is in the nature of ex vivo treatment of the heart with mesenchymal stem cells (AKA: bone marrow stromal cells, marrow stromal cells, MSCs, marrow stroma cells), to improve cardiac function in a patient with heart failure, or to treat cardiac failure. There is no treatment in the art of record with regard to these tissues and the use of MSCs to improve any cardiac function in any patient or any patient with heart failure, much less to treat cardiac failure itself.

The closest art of record regarding the nature of the invention is the use of cardiomyocyte transplantation to improve heart function. Li, et al. (1996) Ann. Thorac. Surg., 62: 654-61. Li demonstrates the transplantation of cardiomyocytes, not MSCs, derived from fetal rat hearts by injection into the scar tissue of rats developed from cryoinjury of the left ventricle four weeks previous to transplantation (p. 655, Col. 1, Last two paragraphs). Here, Li demonstrates that heart function was improved by such treatment over those not injected with the fetal cardiomyocytes through differences in developed pressure at balloon volumes of 0.1 and 0.2 mL, where the cryoinjured group exhibited worse systolic, diastolic, and developed pressures (Figures 6-7 and p. 657-658). However, these fetal cardiomyocytes are not MSCs. They have different physiological characteristics and therefore, Li is not enabling of the use of MSCs.

With regard to the formation of cardiomyocytes from MSCs, Makino, et al. (1999) J. Clin. Invest., 103(5): 697-705, provides the closest art of record. Here, Makino demonstrates that, *in vitro*, immortalized MSCs can be treated with 5-azacytidine to form cells with some characteristics similar to fetal ventricular cardiomyocytes (ABSTRACT). However, Makino similarly does not enable Applicant's claimed invention, because these cells are immortalized, and treated with artificial substances *in vitro*. Therefore, the artisan would not be able to predict that MSCs that are not immortalized would be able to differentiate similarly, because immortalized cells have had changes to their genetic structure to allow them to become immortal. The artisan would also not be able to predict that MSCs, whether immortalized or not, would be able to be treated with enough 5-azacytidine *in vivo* to differentiate, or whether these cells would actually become part of the heart tissue. Also, the Artisan would not be able to reasonably predict that such cells, even if they exhibit the characteristics Makino demonstrates,

would become part of the heart tissue and thereby improve cardiac function, much less treat a failed heart.

Hence, in reviewing the aforementioned nature of the invention, the Artisan would require a showing that transplanted cells reach the effected tissues, forms the characteristics of the tissue which are required to effect treatment, and that such correlated with improvements of cardiac function, or an improvement that resolves cardiac failure.

The State of the Prior Art

The state of the prior art with regard to *ex vivo* therapy is similarly not enabling of new inventions in the field. In Holden, et al. (2002) Science, 296: 2126-29, a recent review in the field, the authors emphasize the ways in which stem cells can effectively fool the Artisan.

For example, in Holden, it is shown that "[C]ells in culture can mutate and develop markers characteristic of other lineages. Cells injected into foreign tissue can take up local DNA – and thus appear to have changed identity – without actually becoming transformed. An introduced macrophage can show the markings of a cell it's eaten." (p. 2126). These are just some of the "multiple ways cells can fool [the investigators]." (Id.). Furthermore, Holden points out, "[the cells transplanted] must be properly identified at the outset, because a single alien cell in ostensibly purified culture could produce misleading results. Putting out a few new proteins does not count, they said; instead, the cells must contribute to the functions of the host tissue: passing electrical signals in the nervous system, or filtering impurities in the liver. This means that a single well-characterized donor cell has to be shown capable of creating a 'robust' population and not just a scattering of cells in the new tissue." (Id., p. 2127).

Lastly, while Wu, et al. (2003) Transplantation, 75(5): 679-85 provides much in the way of optimism for the use of such MSCs to be used in tissue repair of the heart, Wu also demonstrates the state of the art is nowhere near being able to use such cells in any reasonably predictable manner to improve cardiac function or treat heart failure in general. Wu, while demonstrating that such MSCs migrated to the site of allograft rejection, does not show any improvement coincident with such migration (ABSTRACT). In fact, Wu echos some of Holden's concerns, stating "Although we have demonstrated an active migration ... into heart allografts, concern over whether the extensive *in vitro* manipulation of the MSC ... should be discussed. Although we do not have evidence to prove or disprove such a notion, it seems unlikely ...." (CONCLUSIONS).

Consequently, in reviewing the state of the art, and the nature of the invention, the Artisan would require, to make and/or use a new invention in the field of MSCs for improving cardiac function or treating cardiac failure, a showing that enough MSCs would reach the sites required, that such cells would differentiate into, and become a living part of, the myocardial tissues effected, and that such would effect treatment. Alternatively, demonstrations of specific treatments of such conditions with MSCs would enable that specific treatment through that particular route of administration, because, if the method works, it must have met these requirements.

Moreover, because of the generally unenabling nature of the art, absent a largely enabling disclosure by Applicant, by way of specific direction and guidance and/or working examples, the invention claimed is not enabled.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, the Artisan would not have been able to make and/or use the invention claimed without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, does not disclose any therapeutic application of MSCs to effect treatment or improvement of any cardiac function, or treatment of heart failure, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious.

Hence, absent a strong showing of guidance and direction and/or examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses heart failure and a few current theories on treatment (pp. 1-13). More broad discussion is given to the advantages of the invention, methods of transplantation, methods of tracking transplanted cells, and the generally-encouraging, yet non-enabling, results that lead the Applicants to propose their invention (pp. 14-21).

However, such broad discussion does not constitute the specific direction and guidance that the Artisan would require to practice the invention. Specifically, the guidance and direction would not allow the Artisan to reasonably predict that any coronary condition would be treatable through the use of MSCs. The Artisan could not reasonably predict that any cells would reach the effected tissues, differentiate properly, become part of the tissues, and effect treatment.

Without such specific guidance and direction allowing the same, the invention is not enabled without a large showing in the Examples.

The Existence of Working Examples

Example 1 provides a preliminary experiment in which rats were treated by transplantation into the left ventricle wall, with isogenically-derived MSC which had been treated with DAPI. At a later time point, the rat hearts were excised and sectioned. The sections demonstrate that cells with a few characteristics of cardiomyocytes were present. Such characteristics include the development of gap-junction protein, connexin, and the presence of myosin slow protein. However, as indicated above, there are many ways these cells can fool the Artisan. There was no showing that these cells function as part of the myocardium. It is equally possible that these cells fused with other cells, or are simply exhibiting a few characteristics of the myocardium. Moreover, no showing is given of improved cardiac function, and these rats did not suffer from cardiac failure, as the control group did survive. Example 1 also provides a prophetic example, and suggests the measurements to get at improved cardiac function (pp. 29-20); however, the results are simply prophetic and not reasonably predictive of what results would actually be obtained.

Example 2 provides a demonstration of rats that had undergone an induced myocardial infarction by ligation of the left coronary artery. MSCs were then transformed with viral vectors allowing the expression of beta-galactosidase. Such cells appeared to populate the myocardium, including the site of infarct-ischemia, and had some of the characteristics of fibroblasts. However, again, no showing of improved condition is shown, and there is no evidence given that

these cells are not just showing a few of the characteristics of the tissue, rather than actually being part of the tissue.

Hence, the examples are similarly not enabling of the Applicant's invention. They do not demonstrate any improved function or the treatment of heart failure, and they do not demonstrate that the MSCs actually differentiated and became part of the tissue, rather than just demonstrating a few characteristics of the tissue.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the insufficiency of the working examples, the insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, one of skill in the art would be required to perform a large quantity of experimentation to make and/or use the invention as claimed by Applicant.

Such experimentation would be required to determine what routes of administration are required, whether such administered MSCs would actually become part of which tissues in the heart, if any, and then to determine if such cells would reach these tissues in high enough quantities and thereby effect any improvement or treatment of any heart condition at all, much less cardiac failure.

Conclusion

Because of large amount of experimentation required for the Artisan to make and/or use the invention, as claimed by Applicant, such experimentation is considered undue, and therefore, the claims are not enabled.

CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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